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Grapefruit juice-felodipine interaction: reproducibility and characterization with the extended release drug formulation

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1 Felodipine 10 mg extended release was administered with 250 ml regular-strength grapefruit juice or water in a randomized crossover manner followed by a second grapefruit juice treatment in 12 healthy men. The pharmacokinetics of felodipine and primary oxidative metabolite, dehydrofelodipine, were evaluated.

2 Initial grapefruit juice treatment increased felodipine AUC (mean ± s.d.; 56.6 ± 21.9 *vs* 28.1 ± 11.5 ng ml^{-1} h; $P < 0.001$) and C_{max} (8.1 ± 2.5 *vs* 3.3 ± 1.2 ng ml^{-1}; $P < 0.001$) compared with water. Felodipine t_{max} (median; 2.8 *vs* 3.0 h) and $t_{1/2}$ (7.3 ± 3.7 *vs* 6.9 ± 3.6 h) were not altered.

3 Readministration of felodipine with grapefruit juice produced mean felodipine AUC (61.5 ± 32.2 ng ml^{-1} h) and C_{max} (8.4 ± 4.8 ng ml^{-1}) which were similar to the initial grapefruit juice treatment 1–3 weeks previously. Felodipine AUC ($r = 0.73$, $P < 0.01$) and C_{max} ($r = 0.69$, $P < 0.02$) correlated between grapefruit juice treatments among individuals.

4 The % increase in felodipine AUC with the initial grapefruit juice treatment compared with water correlated with the % increase in felodipine C_{max} among individuals ($r = 0.80$, $P < 0.01$). Dehydrofelodipine AUC (74.7 ± 28.7 *vs* 48.5 ± 16.3 ng ml^{-1} h; $P < 0.01$) and C_{max} (12.1 ± 2.9 *vs* 7.9 ± 2.6 ng ml^{-1}; $P < 0.01$) were augmented with grapefruit juice compared with water. The ratios of dehydrofelodipine/felodipine for AUC (1.35 ± 0.26 *vs* 1.78 ± 0.23; $P < 0.001$) and at felodipine C_{max} (1.55 ± 0.35 *vs* 2.33 ± 0.29; $P < 0.001$) were reduced.

5 There was a negative correlation between felodipine AUC with water and the % increase in AUC among individuals with data combined from both grapefruit juice treatments ($r = -0.47$; $P < 0.02$); a similar inverse relation was also found for C_{max} ($r = -0.47$; $P < 0.02$).

6 The interaction was variable among individuals but reproducible within individuals. Grapefruit juice reduced the presystemic elimination of felodipine through inhibition of primary and secondary drug metabolic steps. The increase in felodipine AUC and C_{max} was partially dependent upon the corresponding pharmacokinetic value with water.

Keywords grapefruit felodipine cytochrome P-450 CYP3A4 food-drug interaction slow-release formulation

Introduction

Mealtimes are often recommended for the administration of medications, possibly to aid patient compliance to the treatment regimen [1]. Grapefruit juice is known to interact with several drugs including the dihydropyridine calcium antagonists, felodipine [2–4], nifedipine [2, 5, 6], nitrendipine [7] and nisoldipine [8], as well as cyclosporin [9–12] and terfenadine [13, 14]. The topic has been recently reviewed [15]. In our initial report [2], a glass (250 ml) of double-strength grapefruit juice approximately tripled

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the mean plasma felodipine peak concentration (C_{max}) and area under the drug concentration-time curve (AUC) of the plain tablet through inhibition of presystemic metabolism. These effects doubled blood pressure reduction, heart rate increase and the frequency of adverse effects in borderline hypertensive patients. A subsequent investigation demonstrated that a normal amount of regular-strength grapefruit juice augmented felodipine AUC which corresponded to an increase in drug bioavailability from 15% to 45% and which was nearly the same extent as the double-strength juice [3]. Thus, the interaction between grapefruit juice and felodipine has important implications for pharmacotherapy.

The increase in felodipine AUC and C_{max} was highly variable among individuals. Factors determining this variability have not been defined. In addition, preliminary data suggested that grapefruit juice may produce less interaction with felodipine administered as the extended release formulation compared with the plain tablet [16].

The purpose of this study was to evaluate the reproducibility of the grapefruit juice-felodipine pharmacokinetic interaction during single dose retesting of subjects. The interaction between grapefruit juice and felodipine extended release formulation was also characterized.

This study was presented in part at the Annual Meeting of the Canadian Society for Clinical Investigation, September 14–19, 1994, Toronto, Ontario.

Methods

Study population

Twelve Caucasian men (age range, 18–40 years) were tested. An evaluation before the study showed subjects had normal physical findings, haematologies, serum chemistries and urinalyses. Individuals provided written informed consent for the study which had been approved by the Health Sciences Standing Committee on Human Research at the University of Western Ontario (London, Ontario, Canada).

Experimental protocol

Subjects received racemic felodipine 10 mg extended release (ER) formulation with either 250 ml water or 250 ml regular-strength grapefruit juice (Everfresh Inc., Windsor, Ontario (the same lot number was used throughout the study)). On the initial two study days, felodipine was administered with water or grapefruit juice in a randomized crossover manner. On the third study day, felodipine with grapefruit juice was retested. The interval between retesting with grapefruit juice ranged from 1–3 weeks. Subjects abstained from alcohol for 48 h and fasted for 10 h before testing. Blood was sampled just before dosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0 and 24.0 h. Subjects consumed a standardized lunch at 4 h after administration. Neither beverages containing caffeine nor smoking were allowed but water was permitted from 3 h after drug administration. Plasma concentrations of felodipine and primary metabolite, dehydrofelodipine, were measured by a method employing capillary gas chromatography with electron capture detection [17]. The interday coefficients of variation for plasma felodipine and dehydrofelodipine concentrations at 1.0 ng ml^{-1} were 2.2% and 5.8%, respectively.

Data analysis

Plasma felodipine and dehydrofelodipine concentrations were analysed by a non-compartmental method. The terminal elimination rate constant (λ_z) was determined by log-linear regression of the final data points (at least three). The half-life of the terminal log-linear phase ($t_{1/2,z}$) was calculated as $0.693/\lambda_z$. The AUC was calculated from 0–8 h, 0–24 h and 0 to infinity by the linear trapezoidal method. The extrapolated area was determined by dividing the final concentration by λ_z. Values of C_{max} and t_{max} were obtained directly from the experimental data.

Statistical comparisons among the three groups initially used ANOVA for repeated measures. For those analyses with $P < 0.05$, the effect of grapefruit juice was compared with that of water by paired t-test corrected for multiple comparisons ($P < 0.025$ significant). Data are presented as the mean ± s.d.

Results

Mean plasma felodipine concentration-time curves for the three treatments are shown in Figure 1. Initial grapefruit juice administration increased felodipine concentrations between 2.5 and 24 h. Felodipine

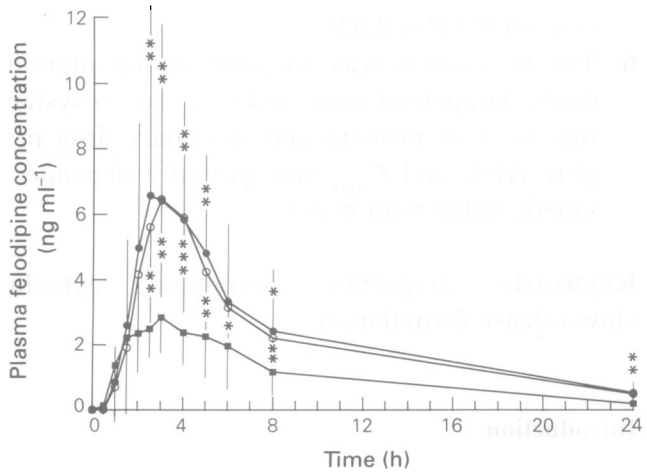

Figure 1 Mean plasma felodipine concentration-time profiles for individuals (n = 12) administered felodipine 10 mg extended release tablet with water (■) or grapefruit juice (first treatment ○, second treatment ●). Bars represent the s.d. Comparisons were made at each measurement time between water and the two grapefruit juice treatments: *$P < 0.025$, **$P < 0.01$, ***$P < 0.001$.

AUC and C_{max} were 225 ± 113% (range, 103–469%, $P < 0.001$) and 270 ± 126% (range, 116–577%, $P < 0.001$), respectively, of those with water (Table 1). The t_{max} and $t_{1/2}$ values were not different between treatments. Retesting with grapefruit juice produced mean felodipine pharmacokinetics that were not different from the results with initial grapefruit juice administration.

Felodipine AUC with the initial grapefruit juice treatment ranged 3.5-fold among individuals and was reproducible on retesting within individuals (Figure 2). There was a significant correlation between the two grapefruit juice treatments for felodipine AUC(0,8h), the period over which plasma drug concentrations were most frequently monitored ($r = 0.91$, $P < 0.001$). It accounted for 82% of the variability among individuals. Felodipine C_{max} with the initial grapefruit juice administration was also reproducible on rechallenge.

The % increase in felodipine AUC with the initial grapefruit juice treatment compared with water correlated with the % increase in felodipine C_{max} among individuals ($r = 0.80$, $P < 0.01$). Dehydrofelodipine AUC and C_{max} following the initial grapefruit juice administration were increased compared with water (Table 2). The ratios of dehydrofelodipine/felodipine for AUC (1.35 ± 0.26 *vs* 1.78 ± 0.23, $P < 0.001$) and at felodipine C_{max} (1.55 ± 0.35 *vs* 2.33 ± 0.29, $P < 0.001$) were reduced with grapefruit juice compared with water.

Felodipine AUC with water was plotted against the % increase in felodipine AUC with both grapefruit juice treatments compared with water among individuals (Figure 3). Felodipine AUC with water ranged three-fold among individuals and correlated negatively with the % increase in felodipine AUC ($n = 24$, $r = -0.47$, $P < 0.02$). The correlation coefficient accounted for 22% of the variability of the interaction among individuals. Felodipine C_{max} with water ranged four-fold and also correlated negatively with the % increase in felodipine C_{max} ($n = 24$, $r = -0.47$, $P < 0.02$).

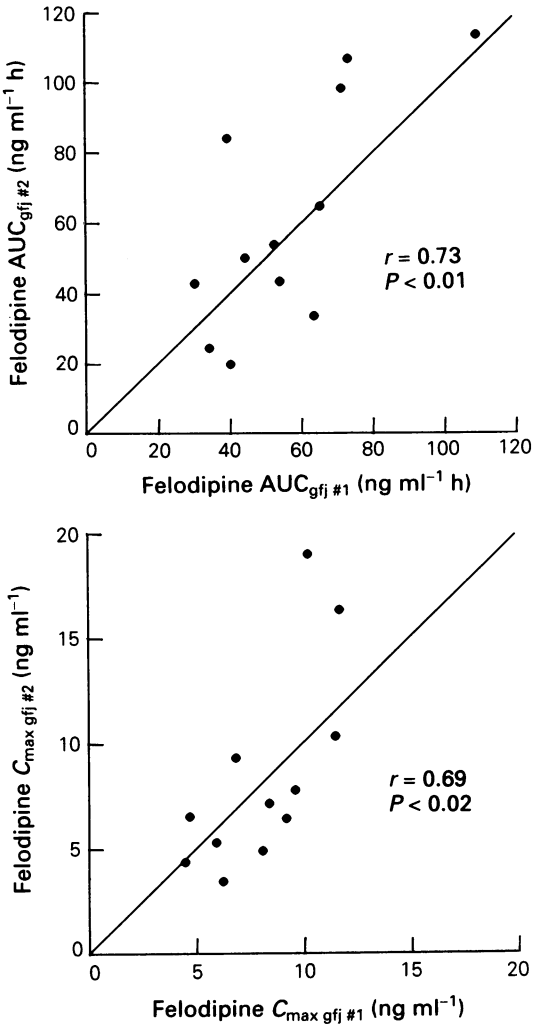

Figure 2 Felodipine AUC (upper graph) and C_{max} (lower graph) with the initial grapefruit juice treatment plotted against the corresponding value with the second grapefuit juice treatment for each individual. Diagonal represents the line of unity.

Table 1 Pharmacokinetics of felodipine with water and both grapefruit juice treatments

	Water (W)	*Grapefruit juice #1 (G1)*	*Grapefruit juice #2 (G2)*	*Mean difference (95% CI)* W vs G1	W vs G2
AUC (ng ml^{-1} h)	28.1 ± 11.5	56.6 ± 21.9***	61.5 ± 32.2**	28.5 (17.5–39.5)	33.4 (16.2–49.7)
C_{max} (ng ml^{-1})	3.3 ± 1.2	8.1 ± 2.5***	8.4 ± 4.8***	4.8 (3.4–6.2)	5.1 (2.6–7.6)
$t_{1/2,z}$ (h)	6.9 ± 3.6	7.3 ± 3.7	8.6 ± 4.6	0.4 (−2.6–3.5)	1.7 (−1.4–4.9)
t_{max} (h)	3.0 (2.0–6.0)	2.8 (2.0–4.0)	2.5 (1.5–5.0)		

Data represent the mean ± s.d. ($n = 12$) except for t_{max} which is median (range).
*$P < 0.025$, **$P < 0.01$, ***$P < 0.001$ compared with water.

Table 2 Pharmacokinetics of dehydrofelodipine with water and initial grapefruit juice administration

	Water	*Grapefruit juice #1*	*Mean difference (95% CI)*
AUC (ng ml^{-1} h)	48.5 ± 16.3	74.7 ± 28.7**	26.2 (13.2–39.1)
C_{max} (ng ml^{-1})	7.9 ± 2.6	12.1 ± 2.9**	4.2 (2.6–5.7)
$t_{1/2,z}$ (h)	7.3 ± 4.5	8.4 ± 3.4	1.1 (−2.0–4.1)
t_{max} (h)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	

Data represent the mean ± s.d. (n = 12) except for t_{max} which is median (range).
*P < 0.025, **P < 0.01, ***P < 0.001 compared with water.

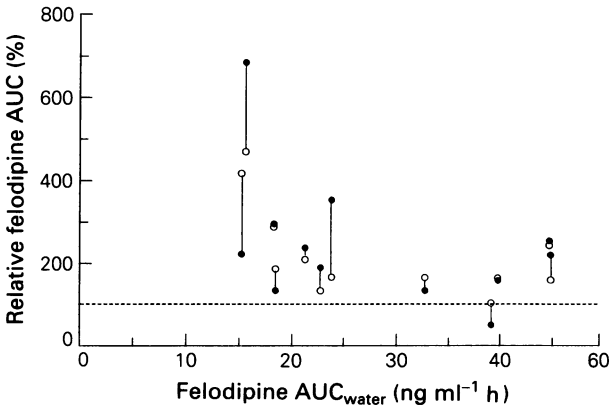

Figure 3 Absolute felodipine AUC with water plotted against relative % felodipine AUC with the two grapefruit juice treatments (1 ○, 2 ●) compared with water. The two values for each individual are joined by a vertical line.

Discussion

Grapefruit juice more than doubled the mean AUC and almost tripled the mean C_{max} of felodipine extended release. The magnitude of the interaction was highly variable among individuals. However, felodipine AUC and C_{max} with grapefruit juice were reproducible within individuals. Thus, determinant(s) of the grapefruit juice-felodipine interaction appear mainly inherent to the individual. Clinically, this suggests that patients with a marked increase in plasma felodipine concentrations with grapefruit juice would be at a risk of a similar large interaction on re-challenge, and *vice-versa*, at least within 1 month of re-exposure.

Preliminary data had suggested that the effect of grapefruit juice may be relatively short lasting possibly because of rapid metabolism of inhibitory components [3]. However, the marked increase in felodipine C_{max} with grapefruit juice with no change in t_{max} suggests that the effect of grapefruit juice lasts for several hours. Prolonged grapefruit juice effect raises the possibility of an interaction with grapefruit juice consumed at some time previous to felodipine administration.

Grapefruit juice produced a proportional increase in felodipine AUC and C_{max} among individuals with no change in the apparent elimination half-life of the extended release formulation in this study. Therefore, the interaction occurred during drug absorption. The decreased proportion of dehydrofelodipine to felodipine with grapefruit juice for AUC and at felodipine C_{max} indicated inhibition of the primary step in felodipine metabolism. The higher dehydrofelodipine AUC and C_{max} with grapefruit juice supported additional inhibition of secondary metabolic steps. These effects are analogous to those previously reported for felodipine plain tablets [2–4]. Thus, grapefruit juice most probably augmented the bioavailability of felodipine extended release by decreasing presystemic drug metabolism.

The primary step of felodipine oxidation is mediated by cytochrome P4503A4 [18] which varies markedly in amount and catalytic activity in liver [19, 20] and intestinal wall [21, 22] among individuals and between these tissues within individuals [22]. In a large population study, absolute felodipine bioavailability ranged eight-fold among individuals as a result of variability in presystemic elimination [23]. Thus, individuals with the highest cytochrome P4503A4 activity in liver and intestinal wall would likely have the lowest felodipine AUC and C_{max}. It might be expected that individuals with the lowest felodipine AUC and C_{max} with water would show the greatest percent increase in these parameters with grapefruit juice which was observed in this investigation. However, baseline felodipine AUC and C_{max} accounted for only 22% of the variability. Although hepatic drug metabolism is often considered of primary importance, intestinal drug metabolism has been shown to play a major role in presystemic felodipine elimination [24, 25]. Also, grapefruit juice did not appear to reduce systemic felodipine elimination.

Therefore, one possible explanation for the low correlation was that grapefruit juice inhibition of felodipine metabolism may be limited to the intestinal wall.

Grapefruit juice-mediated pharmacokinetic changes of the magnitude observed in this study have previously been shown to produce about twice the haemodynamic effects of felodipine taken with water in borderline hypertensive patients [2]. Thus, this interaction also appears clinically relevant for the marketed extended release formulation of this drug. The grapefruit juice-felodipine interaction may be particularly important for patients with severe hypertension as they would show a greater decrease in blood pressure and for patients with stable angina since both can develop ischaemic complications with dihydropyridines leading to myocardial infarction or unstable angina [26–29].

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